Amendments to the Specification

Please replace the paragraph 0014 of US Publication 2002/0061569 with the following:

The gene products implicated in Salmonella pathogenesis include type three secretion systems (TTSS), proteins affecting cytoplasmic structure of the target cells, many proteins carrying out functions necessary for survival and proliferation of Salmonella in the host, as well as "traditional" factors such as endotoxin and secreted exotoxins. Additionally, there must be factors mediating species-specific illnesses. Despite this most of the genomes of S. enterica ser. Typhi ~~(see http://www.sanger.ac.uk/Proiects/S_typhi/ for the genome database)~~ and S. enterica ser. Typhimurium ~~(see http://genome.wustl.edu/gsc/bacterial/salm- onella.shtml for the genome database)~~ are highly conserved and are mutually useful for gene identification in multiple serovars. The Salmonella are a complex group of enteric bacteria causing disease similar to but distinct from other gram-negative enterics such as E. coli and have been a focus of biomedical research for the last century.

Please replace the paragraph 0441 of US Publication 2002/0061569 with the following:

By "homologous coding nucleic acid" is meant a nucleic acid homologous to a nucleic acid encoding a gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 8-3795 or a portion thereof. In some embodiments, the homologous coding nucleic acid may have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 3796-3800, 3806-4860, 5916-10012 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive

nucleotides thereof. In other embodiments the homologous coding nucleic acids may have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequences complementary to one of SEQ ID NOs.: 8-3795 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. Identity may be measured using BLASTN version 2.0 with the default parameters or tBLASTX with the default parameters. (Altschul, S. F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997), the disclosure of which is incorporated herein by reference in its entirety) Alternatively a "homologuous coding nucleic acid" could be identified by membership of the gene of interest to a functional orthologue cluster. All other members of that orthologue cluster would be considered homologues. ~~Such a library of functional orthologue clusters can be found at http://www.ncbi.nlm.nih.gov/COG.~~ A gene can be classified into a cluster of orthologous groups or COG by using the COGNITOR program available at the above web site, or by direct BLASTP comparison of the gene of interest to the members of the COGs and analysis of these results as described by Tatusov <u>et al.</u>, ~~R. L., Galperin, M. Y., Natale, D. A. and Koonin, E. V.~~ (2000) <u>"</u>The COG database: a tool for genome-scale analysis of protein functions and evolution.<u>"</u> Nucleic Acids Research ~~v. 28 n. 1, pp33-36~~ <u>28:33</u>.

Please replace the paragraph 0478 of US Publication 2002/0061569 with the following:

The number of nucleotide and protein sequences available in database systems has been growing exponentially for years. For example, the complete nucleotide sequences of Caenorhabditis elegans and several bacterial genomes, including E. coli, Aeropyrum pernix, Aquifex aeolicus, Archaeoglobus fulgidus, Bacillus subtilis, Borrelia burgdorferi, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium tetani, Corynebacterium diptheria, Deinococcus radiodurans, Haemophilus influenzae, Helicobacter pylori 26695, Helicobacter pylori J99, Methanobacterium thermoautotrophicum, Methanococcus jannaschii, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Pseudomonas aeruginosa, Pyrococcus abyssi, Pyrococcus horikoshii, Rickettsia prowazekii, Synechocystis PCC6803, Thermotoga maritima, Treponema pallidum, Bordetella pertussis, Campylobacter jejuni, Clostridium acetobutylicum, Mycobacterium tuberculosis CSU#93, Neisseria gonorrhoeae, Neisseria meningitidis, Pseudomonas aeruginosa, Pyrobaculum aerophilum, Pyrococcus furiosus, Rhodobacter capsulatus, Salmonella typhimurium, Streptococcus mutans, Streptococcus pyogenes, Ureaplasma urealyticum and Vibrio cholera are available. This nucleotide sequence information is stored in a number of databanks, such as GenBank, the National Center for Biotechnology Information (NCBI), the Genome Sequencing Center ~~(http:Hlgenome.wustl.edu/gsc/salmonella.shtml)~~, and the Sanger Centre ~~(http://www.sanger.ac.uk/projects/S_typhi)~~ which are publicly available for searching.

Please replace the paragraph 0482 of US Publication 2002/0061569 with the following:

In one embodiment of the present invention, an operon is identified and then dissected to determine which gene or genes are required for proliferation. Operons can be identified by a variety of means known to those in the art. For example, the RegulonDB DataBase described by Huerta et al. (Nucl. Acids Res. 26:55-59, 1998), ~~which may also be found on the website http://www.cifn.unam.mx/Computational_Biology/regulondb/, the disclosures of which are incorporated herein by reference in their entireties~~, provides information about operons in Escherichia coli. The Subtilist database ~~(http://bioweb.pasteur.fr/GenoList/SubtiList), (Moszer, I., Glaser, P. and Danchin, A. (1995) Microbiology 141: 261-268 and Moszer, 1 (1998) FEBS Letters 430: 28-36, the disclosures of which are incorporated herein in their entireties)~~ <u>(Moszer et al., 1995, "SubtiList: a relational database for the *Bacillus subtilis* genome" Microbiology 141:261-268 and Moszer et al., 1998, "The complete genome of *Bacillus subtilis*: From sequence annotation to data management and analysis" *FEBS Letters* 430:28-36)</u>, may also be used to predict operons. This database lists genes from the fully sequenced, Gram-positive bacteria, Bacillus subtilis, together with predicted promoters and terminator sites. This information can be used in conjunction with the Staphylococcus aureus genomic sequence data to predict operons and thus produce a list of the genes affected by the antisense nucleic acids of the present invention. The Pseudomonas aerginosa web site ~~(http://www.pseudomonas.com)~~ can be used to help predict operon organization in this bacterium. The databases available from the Genome Sequencing Center ~~(http:/Hgenome.wustl.edu/gsc/salmonella-.shtml)~~, and the Sanger Centre ~~(http:/Hwww.sanger.ac.uk/projects/S typhi)~~ may be used to predict operons in Salmonella typhimurium. The TIGR microbial database has an incomplete version of the E. faecalis genome

~~http://www.tigr.org/cgi-bin/BlastSearch/blast.cai?organism=_e faecalis~~. One can take a nucleotide sequence and BLAST it for homologs.

Please replace the paragraph 0523 of US Publication 2002/0061569 with the following:

In the case of Staphylococcus aureus, a novel inducible promoter system, XylT5, comprising a modified T5 promoter fused to the xylO operater from the xyla promoter of Staphylococcus aureus was used. The promoter is described in ~~U.S. Provisional Patent Application Ser. No. 60/259,434~~ International Publication No. WO 2002/051982, the disclosure of which is incorporated herein by reference in its entirety. Transcription from this hybrid promoter is inducible by xylose.

Please replace the paragraph 0600 of US Publication 2002/0061569 with the following

The nucleotide sequences of the subcloned fragments from Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumoniae, Pseudomonas aeruginosa or Enterococcus faecalis obtained from the expression vectors discussed above were compared to known sequences from Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumoniae, Pseudomonas aeruginosa or Enterococcus faecalis and other microorganisms as follows. First, to confirm that each clone originated from one location on the chromosome and was not chimeric, the nucleotide sequences of the selected clones were compared against the Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumoniae, Pseudomonas aeruginosa or Enterococcus faecalis genomic sequences to align the clone to the correct position on the chromosome. The NCBI BLASTN v 2.0.9 program was used for this comparison, and the incomplete Staphylococcus aureus genomic sequences licensed from TIGR, as well as the NCBI nonredundant GenBank database were used as the source of genomic data. Salmonella typhimurium sequences were compared to sequences available from the Genome Sequencing Center~~ (http://genome.wustl.edu/gsc/salmonella.shtml),~~ and the Sanger Centre ~~(http://www.sanger.ac.uk/projects/S_typhi)~~. Pseudomonas aeruginosa sequences were compared

to a proprietary database and the NCBI GenBank database. The E. faecalis sequences were compared to a proprietary database.

Please replace the paragraph 0630 of US Publication 2002/0061569 with the following:

Alternatively, ORFs were identified and refined by conducting a survey of the public and private data sources. Full-length gene protein and nucleotide sequences for these organisms were assembled from various sources. For Pseudomonas aeruginosa, gene sequences were adopted from the Pseudomonas genome sequencing project (see e.g., Winsor et al., 2009, "Pseudomonas Genome Database: facilitating user-friendly, comprehensive comparisons of microbial genomes" Nucleic Acids Research 37:D483-488) ~~(downloaded from http://www.pseudomonas.com)~~. For Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae and Salmonella typhi, genomic sequences from PathoSeq v 4.1 (Mar 2000 release) was reanalyzed for ORFs using the gene finding software GeneMark v 2.4a, which was purchased from GenePro Inc. 451 Bishop St., N. W., Suite B, Atlanta, Ga., 30318, USA.

Please replace the paragraph 0635 of US Publication 2002/0061569 with the following:

It will be appreciated that ORFs may also be identified using databases other than PathoSeq. For example, the ORFs may be identified using the methods described in ~~U.S. Provisional Patent Application Ser. No. 60/191,078, filed Mar. 21, 2000~~ International Publication No. WO 2001/70955, the disclosure of which is incorporated herein by reference in its entirety.

Please replace the paragraph 0637 of US Publication 2002/0061569 with the following:

Operons are predicted by looking for all adjacent genes in a genomic region that lie in the same orientation with no large noncoding gaps in between. First, full-length ORFs complementary to the antisense molecules are identified as described above. Adjacent ORFs are then identified and their relative orientation determined either by directly analyzing the genomic sequences surrounding the ORFs complementary to the antisense clones or by extracting

adjacent ORFs from the collection obtained through whole genome ORF analysis described above followed by ORF alignment. Operons predicted in this way may be confirmed by comparison to the arrangement of the homologous nucleic acids in the Bacillus subtilis complete genome sequence (see Moszer et al., 1995, "SubtiList: a relational database for the *Bacillus subtilis* genome" Microbiology 141:261-268 and Moszer et al., 1998, "The complete genome of *Bacillus subtilis*: From sequence annotation to data management and analysis" *FEBS Letters* 430:28-36)~~, as reported by the genome database compiled at Institut Pasteur Subtilist Release RI 5.1 (Jun. 24, 1999) which can be found at htt ://bioweb.pasteur.fr/GenoList/SubtiList/~~. The Bacillus subtilis genome is the only fully sequenced and annotated genome from a Gram-positive microorganism, and appears to have a high level of similarity to Staphylococcus aureus both at the level of conservation of gene sequence and genomic organization including operon structure. Operons for Salmonella typhimurium and Klebsiella pneumoniae may be identified by comparison with E. coli, Haemophilus, or Pseudomonas sequences (see e.g., Winsor et al., 2009, “Pseudomonas Genome Database: facilitating user-friendly, comprehensive comparisons of microbial genomes” Nucleic Acids Research 37:D483-488). ~~The Pseudomonas aeruginosa web site (http://www.pseudomonas.com) can also be used to help predict operon organization in this bacterium.~~

Please replace the paragraph 0776 of US Publication 2002/0061569 with the following:

As a demonstration of the methodology required to find homologues to an essential gene, nine prokaryotic organisms were analyzed and compared in detail. First, the most reliable source of gene sequences for each organism was assessed by conducting a survey of the public and private data sources. The nine organisms studied are Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae and Salmonella typhi. Full-length gene protein and nucleotide sequences for these organisms were assembled from various sources. For Escherichia coli, Haemophilus influenzae and Helicobacter pylori, gene sequences were adopted from the public sequencing projects, and derived from the GenPept 115 database (available from NCBI). For Pseudomonas aeruginosa, gene sequences were adopted from the Pseudomonas genome

sequencing project (see e.g., Winsor et al., 2009, "Pseudomonas Genome Database: facilitating user-friendly, comprehensive comparisons of microbial genomes" Nucleic Acids Research 37:D483-488) ~~(downloaded from http://www.pseudomonas.com)~~. For Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae and Salmonella typhi, genomic sequences from PathoSeq v 4.1 (Mar 2000 release) was reanalyzed for ORFs using the gene finding software GeneMark v 2.4a, which was purchased from GenePro Inc. 451 Bishop St., N.W., Suite B, Atlanta, Ga., 30318, USA.